GALECTIN-3 IN CRITICALLY ILL PATIENTS WITH SEPSIS AND/OR TRAUMA: A GOOD PREDICTOR OF OUTCOME OR NOT?

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GALEKTIN - 3 KOD KRITIČNO OBOLELIH PACIJENATA SA SEPSOM I/ILI TRAUMOM: DOBAR PREDIKTOR ISHODA ILI NE?

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ABSTRACT

Severe sepsis and/or trauma complicated with multiple organ dysfunction syndrome are leading causes of death in critically ill patients. The aim of this prospective, observational, single centre study was to assess the prognostic value of galectin-3 regarding outcome in critically ill patients with severe trauma and/or severe sepsis. The outcome measure was hospital mortality.

In total, 75 critically ill patients who were admitted to the intensive care unit of the tertiary university hospital were enrolled in a prospective observational study. Blood samples were collected upon fulfilling Sepsis-3 criteria and for a traumatized Injury Severity Score > 25 points.

Levels of galectin-3 were significantly higher in nonsurvivors on the day of enrolment – Day 1 ($p<0.05$). On Day 1, the area under the curve (AUC) for the galectin-3 for lethal outcome was 0.602. At a cut-off level of 262.82 ng/mL, the sensitivity was 53%, and the specificity was 69.7%, which was objectively determined by a Youden index of 0.20.

The discriminative power of galectin-3 in predicting outcome was statistically significant. Galectin-3 on Day 1 is a fairly good predictor of lethal outcome.

Keywords: *galectin-3; critical care; outcome; hospital mortality*

SAŽETAK

Teška sepsa i/ili trauma kod koje se kao komplikacija javlja sindrom multiple organske disfunkcije je vodeći uzrok smrti kod kritično obolelih. Cilj ove prospektivne, observacione studije je bio da se proceni prognostička vrednost galektina – 3 u smislu ishoda kod kritično obolelih sa teškom traumom i/ili teškom sepsom. Mera ishoda je bio hospitalni mortalitet.

75 kritično obolelih pacijenta, primljenih u jedinicu intenzivne terapije tercijarne univerzitetske bolnice, obuhvaćeno je prospektivnom, observacionom studijom. Uzorci krvi su sakupljani na dan ispunjavanja SEPSIS-3 kriterijuma, a kod traumatizovanih ISS >25 bodova.

Vrednosti galektina – 3 su bile statistički značajno veće kod umrlih na dan uključenja u studiju – Dan 1 ($p<0.05$). Vrednost AUC/ROC za galektin – 3 prvog dana u smislu predikcije ishoda je bila 0.602. Pri cut-off vrednosti od 262.82 ng/mL senzitivnost je bila 53% a specifičnost 69.7%, što je objektivno utvrđeno korišćenjem Youden indeksa čija vrednost je bila 0.20.

Vrednost galektina – 3 prvog dana je dobar prediktor letalnog ishoda.

Ključne reči: *galektin - 3; kritično oboleli; ishod; hospitalni mortalitet*

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INTRODUCTION

Critical illness is defined by the presence of altered organ function in acutely ill patients such that homeostasis cannot be maintained without medical intervention in intensive care units, such as mechanical ventilation, vasoactive support for haemodynamicsa, and renal replacement therapy. It usually involves two or more organ systems. Immune dysfunction is common in critically ill patients, and it may modulate the immune response and affect patient morbidity and mortality, particularly in severe trauma and/or sepsis. Immune cells and mediators, in the critical care setting, are understudied and do represent a challenging area. Inflammatory mediators can be predictive biomarkers of organ dysfunction and outcome in critically ill patients, so they are of interest for both researchers and clinicians (1). One of the most interesting mediators, galectin-3, belongs to a family of conserved proteins with carbohydrate-recognition domains (CRDs). CRDs bind beta-galactosidase, and they consist of approximately 130 amino acids. Galectin-3 is unique in this family of proteins because it is a chimaera-type with two terminals: a C-terminal CRD and an N-terminal that is a protein-binding domain (2, 3, 4).

It is difficult to find adequate biomarkers of the immune response in critical illness, regardless of its cause, with good predictive value regarding outcome because there is a wide and complex array of immune-related mediators. Many of them were explored in this clinical setting (5, 6, 7). Recently, in a few studies, galectin-3 has been investigated as a novel potential biomarker regarding its accuracy and clinical usefulness.

The aim of our prospective observational study was to assess the prognostic value of galectin-3 regarding outcome in a cohort of critically ill patients with secondary sepsis and/or trauma. The outcome measure was hospital mortality.

PATIENTS AND METHODS

Ethical Approval

Approval in concordance with the Declaration of Helsinki was obtained from the local ethics committee, and informed consent was obtained from a patient or first-degree relative.

Patients and study design

A total of 75 critically ill and injured patients, admitted to the surgical intensive care unit (SICU) were enrolled in a prospective study conducted in a tertiary university hospital (Military Medical Academy, Belgrade, Serbia). Patients with secondary sepsis (underlying conditions were peritonitis, pancreatitis and trauma) were enrolled if they had fulfilled current Sepsis-3 diagnostic criteria for sepsis (formerly severe sepsis) and/or septic shock (acute change in total SOFA score ^{3} 2 points and vasopressors required to maintain mean arterial pressure ^{3} 65 mmHg and serum lactate level > 2 mmol/L despite adequate volume resuscitation) (8). The diagnostic criteria encompass any of the following variables thought to be a result of the infection: sepsis-induced hypotension, lactate levels greater than 2 mmol/L, urine output less than 0.5 mL/kg/hr for more than two hours despite adequate fluid resuscitation, acute lung injury with PaO_2/FiO_2 less than 250, creatinine greater than 2.0 mg/dL (176.8 micromol/L), bilirubin greater than 2.0 mg/dL (34.2 micromol/L), platelet count less than 100,000 and coagulopathy (international normalised ratio – INR) greater than 1.5. Additionally, critically ill patients with severe trauma [Injury Severity Score – ISS (determined using Abbreviated Injury Scale – AIS) > 25 points] were enrolled. Only adult patients, at least 18 years of age, were recruited. The exclusion criteria were as follows: (1) secondary sepsis and/or septic shock with an underlying condition other than severe peritonitis, pancreatitis or trauma; (2) malignant disease of any origin; (3) long-term SICU stay before criteria fulfilment; (4) pre-existing immunodeficiency. The Sequential Organ Failure Assessment (SOFA) score, the Simplified Acute Physiology Score (SAPS) II and the Acute Physiology and Chronic Health Evaluation (APACHE) II score were calculated and recorded within the first 24 h after admission to the SICU.

Sampling and analysis

Patient's venous blood was drawn by trained, qualified phlebotomists on the first day of enrolment in the study. The concentration of galectin-3 was determined with the Quantikine Human Galectin-3 Immunoassay ELISA test (R&D Systems Europe Ltd, UK). This assay employs the quantitative sandwich enzyme immunoassay technique. Briefly, a solution of a monoclonal antibody specific for human galectin-3 was prepared according to the manufacturer guidelines. Polystyrene microplates (96 wells; 12 strips of 8 wells) were coated with a prepared solution of monoclonal antibody specific for human galectin-3 (100 µl/well, overnight, + 4 °C). After the washing and blocking procedure, the wells were filled with 100 µl assay diluent and subsequently with 50 µl of standards, controls and samples per appropriate well. Plates were covered and incubated for 2 hours at RT. After another washing procedure, the wells were filled with 200 µl of prepared human galectin-3 conjugate and were covered and incubated for an additional 2 h at RT. After the final washing procedure, 200 µl of substrate solution was placed in each well, and the plate was incubated for 30 min at RT, protected from light. Development of the colour reaction was terminated with stop solution (50 µl/well), and the optical density of each well was determined at 450 nm in a microplate reader (BioTek Synergy HT, Winooski, Vermont, USA)T. The concentrations of the tested samples were obtained by

Table 1. Demographic and clinical data

Total no. of patients	75
Age (average, range)	59.2 (from 18 to 85 yrs)
Sex, n (%) male female	 45 (60.0%) 30 (40.0%)
Simplified Acute Physiology Score II – SAPS II score, mean ± SD	55.23 ± 8.25
Acute Physiology and Chronic Health Evaluation II – APACHE II score, mean ± SD	24.25 ± 4.23
Sequential Organ Failure Assessment – SOFA score, mean ± SD	6.78 ± 2.42
Overall hospital mortality	45.3%

plotting the mean absorbance for each standard on the y-axis against the concentration on the x-axis, from a best fit curve through the points on a log/log graph.

Statistical analysis

A complete statistical analysis of the data was performed with the statistical software package, SPSS Statistics 18. Variables were presented as the mean value ± standard deviation (SD), median, minimal and maximal values. The Kolmogorov-Smirnov test was used for evaluation of the distribution of the data. Statistical significance between groups was tested by Kruskal-Wallis or Mann-Whitney tests. ROC curves were constructed to determine the sensitivity and specificity of mediators for the prediction of outcome. The Youden's index (J), the difference between the true positive rate and the false positive rate, was used. Maximizing this index allows one to find, from the ROC curve, an optimal cut-off point independently from the prevalence. All the analyses were estimated at $p<0.05$ level of statistical significance.

RESULTS

Demographic and clinical data of 75 patients is shown in Table 1.

Baseline characteristics of the patient population regarding galectin-3 according to outcome (hospital mortality) are shown in Table 2.

We compared levels of galectin-3 between survivors and nonsurvivors on Day 1. Levels of galectin-3 were significantly higher in nonsurvivors (Mann-Whitney U Z = -1.972; $p<0.05$). Data are shown in Figure 1.

The clinical accuracy of galectin-3 in predicting outcome was investigated. The discriminative power of this mediator in predicting lethal outcome was statistically significant. A receiver operator curve was generated to determine the cut-off values for optimal sensitivity and specificity for the galectin-3 levels on Day 1. The results are shown in Table 3.

Table 2. Baseline characteristics of the patient population regarding galectin-3 according to outcome

Galectin-3 (ng/mL)	Survivors	Nonsurvivors
N	41	34
Mean	211.20	425.33
Standard Deviation	110.45	715.18
Median	190.25	282.57
Minimum	53	97
Maximum	742	7945

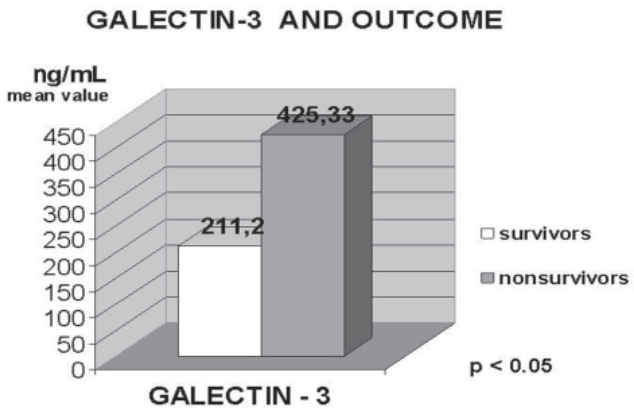

Figure 1.

Table 3. Clinical accuracy of galectin-3 in predicting lethal outcome on Day 1

Parameter	AUC ROC	*p* value	95% Confidence Interval		Cut-off value	Sensitivity (%)	Specificity (%)	Youden index
			Lower Bound	Upper Bound				
Galectin – 3 on Day 1	0.602	p< 0.05	0.547	0.850	262.82	53.0	69.7	0.20

A galectin-3 level that is higher than the cut-off value on Day 1 is a good predictor of lethal outcome in this patient population.

DISCUSSION

Galectin-3 can be found in a variety of tissues and is highly expressed on myeloid cells (like monocytes, macrophages and neutrophils) as well as on epithelial and endothelial cells. After various stimuli, these cells release this mediator, so galectin-3 can be found extracellularly. In our cohort of 75 critically ill and injured patients, we compared levels of galectin-3 between survivors and nonsurvivors. The analysis was performed on the first day of enrolment in the study. The outcome measure was hospital mortality. That is, that these patients were followed for a rather long time (greater than one year) until either hospital discharge or death. Levels of galectin-3 were significantly higher in nonsurvivors. The clinical accuracy of galectin-3 in predicting outcome was investigated. The discriminative power of this mediator in predicting lethal outcome was statistically significant with an AUC/ROC of 0.602. A galectin-3 level higher than the cut-off value of 262.82 pg/mL on Day 1 is a good predictor of lethal outcome in this patient population with a moderate sensitivity of 53% and a rather good specificity of almost 70%.

Free extracellular galectin-3 is involved in immunity against pathogens, in various stages of inflammation with complex roles (9, 10). Recently, it has been shown that galectin-3 can recognize microbial structures (PAMPs – pathogen-associated molecular patterns); also it can be released by damaged tissues, so it serves as a DAMP - damage-associated molecular pattern (11). Galectin-3 is a proinflammatory mediator, so one of its properties is to enhance infiltration of the site of infection with neutrophils and other immunocompetent cells. Galectin-3 is synthesized and stored in the cytoplasm, and it can be either secreted by activated cells or passively released from dying cells. In addition to being a potential DAMP, galectin-3 can act as a PRR - pattern-recognition receptor, so it can modulate innate immunity (12).

Various pathogens are inducers of galectin-3 synthesis and release. Therefore, this glycan binding protein secretion is upregulated by bacteria and fungi. Additionally, it has been shown that this lectin can bind to pathogens. In their study, Quattroni and co-authors, investigated the interaction between galectin-3 and *Neisseria meningitidis*, an important extracellular human pathogen that is a leading cause of meningitis, which can also be complicated by onset of meningococcal sepsis (13). The authors demonstrated by immunohistochemical analysis that galectin-3 is expressed during meningococcal disease and colocalizes with bacterial colonies in infected tissues from patients. They also found that galectin-3 binds to *Neisseria meningitidis*. In animal studies, they used galectin-3 deficient (Gal-3(-/-)) mice to evaluate the contribution of galectin-3 to meningococcal bacteraemia and found that Gal-3(-/-) mice had significantly lower levels of bacteraemia compared with wild-type mice after challenge with live bacteria, indicating that galectin-3 confers an advantage to *Naisseria meningitidis* during systemic infection. It has been shown that expression of galectin-3 influences the course of infection of *Mycobacterium leprae*. Among other things, it diminished the ability of monocytes to differentiate into dendritic cells in response to granulocyte-macrophage colony-stimulating factor – GM-CSF. Additionally, the ability of dendritic cells, which are derived from monocytes, to stimulate T-cell proliferation in response to mycobacterial antigens was also hampered (14). Therefore, in intracellular infection with Mycobacterium, activation of T lymphocytes was affected by high expression of galectin-3. In that scenario, the cell-mediated adaptive immune response, which is necessary to control infection, is inadequate.

As mentioned before, a variety of lectins serve as pattern-recognition receptors during innate immune responses against pathogens, including ficolins and collectins which are soluble molecules (15), as well as C-type lectin family members, which are membrane receptors. Researchers demonstrated that galectin-3 serves as a pattern recognition receptor for bacteria (binds LPS – lipopolysaccharide-endotoxin from *Escherichia coli* and *Pseudomonas aeruginosa*, for instance), virus, fungi and parasites (16). Interestingly, elevated release of galectin-3 can exacerbate tissue damage through activated leukocyte infiltration but can also bind lipopolysaccharide, thus, acting as a negative regulator of endotoxic shock induced by lipopolysaccharide.

Galectin-3 is synthesized and released by a myriad of immune cells acting such as sentinels. This interesting mediator affects immunocompetent cells in an autocrine and/or paracrine fashion, i.e., if it is extracellular, galectin-3 binds to a membrane receptor, and if it is intracellular, galectin-3 modulates intracellular proteins activity. One study showed that injection of exogenous galectin-3 induced migration of neutrophils to the injection site, although, in vitro, galectin-3 is not a neutrophil chemoattractant (17). This suggests that, after being released from cells, galectin-3 does indirectly induce migration of neutrophils acting as a DAMP. It has to be emphasized that galectin-3 does not only enhance neutrophil infiltration of the inflammation site, but it also plays a role in terminating the inflammatory response by being a part of the neutrophil removal process. It has been demonstrated recently, in an animal model of self-resolving peritonitis, that galectin-3-deficient mice exhibited reduced apoptosis and efferocytosis of neutrophils (18). In cell biology, efferocytosis (from efferre, Latin for 'to take to the grave', 'to bury') is the process by which dying/dead cells (e.g., apoptotic or necrotic) are removed by phagocytic cells. It can be regarded as the 'burying of dead cells'. theTherefore, the authors of this study showed the existence of impaired neutrophil clearance without galectin-3 being present.

One of the many roles of galectin-3, the only chimeric galectin, is to act as an alarmin. That was investigated by Mishra and co-authors in animal model of pulmonary infection with *Francisella novicida* (19). As extensive cell death is pivotal in severe infection, the authors focused on host endogenous molecules called alarmins released from dead or dying host cells leading to a proinflammatory response. The authors demonstrated an upregulated expression and extracellular release of galectin-3 in the lungs of mice undergoing lethal pulmonary infection with a virulent strain of *F. novicida* but not in those infected with a non-lethal, attenuated strain of the bacteria. In comparison with their wild-type counterparts, *Francisella novicida*-infected galectin-3-deficient (galectin-3(-/-)) mice demonstrated significantly reduced leukocyte infiltration, particularly neutrophils in their lungs. They also exhibited a marked decrease in inflammatory cytokines, vascular injury markers, and neutrophil-associated inflammatory mediators. *Francisella novicida*-infected galectin-3(-/-) mice exhibited improved lung architecture with reduced cell death and improved survival over wild-type mice, despite similar bacterial burden. The authors concluded that galectin-3 acts as an alarmin by augmenting the inflammatory response.

The effect of galectin-3 on immune cells is, as described above, versatile. As far as mononuclear phagocytes are concerned, one study demonstrated that in microglia (mononuclear phagocytes of central nervous system), galectin-3 functions as an endogenous paracrine ligand for Toll-like receptor (TLR)-4, and so, it induces important TLR-4-mediated activation of the immune cascade (20). Galectin-3-TLR-4 interaction was further confirmed in a murine neuroinflammatory model (intranigral lipopolysaccharide-LPS injection). Dendritic cells are a crucial link between innate and adaptive immunity as they play a pivotal role in determining the Th1/Th2/Th17 polarization of the adaptive immune response. Intracellular galectin-3 predominantly modulates cytokine release by dendritic cells. It has been shown that neutralizing antibodies against this chimeric galectin did not reverse its effects; the evidence is, therefore, pointing to crucial participation of intracellular galectin-3 in the regulation of cytokine release by dendritic cells (21).

Surprisingly, there are only a few studies and a paucity of clinical data regarding galectin-3, a complex multifaceted molecule, as a predictor of infection and/or outcome in critically ill and injured patients. This mediator has dual roles as both a circulating DAMP and a cell membrane-associated PRR. ten Oever and co-workers focused their investigation on assessing the potential of circulating galectin-3 for discriminating between infections and non-infectious inflammatory disorders on the one hand, and between fungal and bacterial infections on the other (22). Galectin-3 was measured in the plasma of 127 patients with either non-infectious inflammatory disorders (gout, autoinflammatory syndrome or pancreatitis) or an infection (viral lower respiratory tract infection, bacterial sepsis or candidaemia). Circulating galectin-3 concentrations were increased in patients with infections when compared with healthy volunteers or patients with non-infectious inflammatory diseases. The clinical accuracy of predicting infection was also assessed. Galectin-3 was a good predictor of infection with AUC/ROC of 0.73. At cut-off value of 20.6 ng/ml specificity was 95%, and sensitivity was 43%. Galectin-3 concentrations were similar in patients with bacterial and Candida sepsis, while being lower in viral respiratory infections. So, galectin-3 could not discriminate between bacterial and fungal sepsis. Another study investigated galectin-3 as a diagnostic marker with opposite results. Mueller and co-workers evaluated to which extent plasma concentrations of galectin-3, among other biomarkers, is increased in heart failure compared with diverse non-cardiac conditions such as infectious disease or chronic kidney disease (23). Compared to healthy controls, the median galectin-3 concentration was a ~1.5-fold increase in patients with heart failure; a ~1.4-fold in pneumonia; a ~2.4-fold in heart failure with pneumonia; a ~2.5-fold in renal disease, and a ~2.7-fold in sepsis ($p<0.001$ for all compared to controls). Galectin-3 was not significantly increased in chronic obstructive pulmonary disease. The authors concluded that, because increased plasma concentrations of galectin-3 are not specific for a distinct disease group, this biomarker is not useful for diagnostic purposes.

Only rather recently, focus regarding galectin-3 has changed towards its outcome predictive value in critical care medicine, i.e., in a patient population similar to ours. Dieplinger and co-workers conducted a study aimed to assess prognostic value, for the prediction of 90-day all-cause mortality, of several biomarkers, including galectin-3, in an unselected cohort of critically ill patients (24). In univariate analyses, increased galectin-3 plasma concentrations at baseline were strong prognostic markers. Last year, Kim and co-workers investigated whether a biomarker could be objective and reliable tool to predict mortality in sepsis and explored the prognostic utility of emerging biomarker galectin-3 regarding the prediction of mortality in patients with sepsis (25). In this retrospective study, 157 septic patients were included. Procalcitonin (PCT), presepsin, galectin-3, and soluble suppression of tumourigenicity 2 (sST2) concentrations were analysed in relation to the 30-day all-cause mortality. Median values of galectin-3 were significantly higher in nonsurvivors (58.6 vs. 24.5 respectively). Our findings are in line with both of these studies (Deplinger et al.; Kim et al.). The trend is the same; nonsurvivors had higher values of galectin-3 than survivors. Levels of galectin-3, in both survivors and nonsurvivors in these two studies, were lower than in our study. That can be explained by the fact that our patients had more severe critical illness, which is reflected by a higher SAPS II score in our patient population when compared to results published by Deplinger et al. Additionally, our patients were obviously sicker, with a hospital mortality rate which was almost doubled compared to the results demonstrated by Kim and co-workers (45.3% vs. 25.5%, respectively). The clinical accuracy of galectin-3

in predicting a lethal outcome on Day 1 was statistically significant in both of these studies, as it was as in ours, with a slightly higher AUC/ROC of 0.7 compared to our AUC/ROC of 0.6. As far as the study published by Kim et al. is concerned, we have to bear in mind that we calculated the clinical accuracy of this mediator in predicting hospital mortality, so the outcome measure was different (in their study it was 30-day mortality).

The complexity of the myriad of galectin-3 activities also makes this mediator very interesting as a biomarker in a variety of fields, such as heart failure (26), kidney diseases (27, 28) and malignant diseases (29, 30).

CONCLUSION

We demonstrate that galectin-3 is an emerging prognostic biomarker in critically ill patients. The levels of galectin-3 were significantly higher in nonsurvivors. The clinical accuracy of galectin-3 in predicting a lethal outcome in critically ill and injured patients was assessed. The discriminative power of this mediator in predicting a lethal outcome, with the outcome measure being hospital mortality, was statistically significant. Trends and patterns in the investigated biomarker that we found should be validated in a larger patient population, so further studies are warranted.

CONFLICT OF INTEREST

No conflicts of interest, financial or otherwise, are declared by the authors.

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